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## Lopinavir pharmacokinetics in COVID-19 patients

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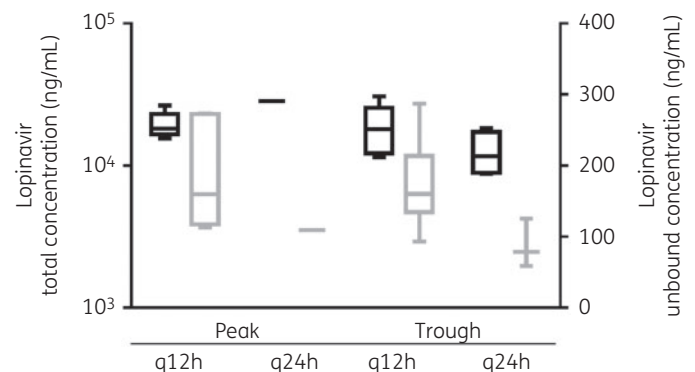
Sir,  
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in late 2019. Therapeutic solutions are currently being tested for COVID-19, the SARS-CoV-2-associated pneumonia. Ritonavir-boosted lopinavir is included in the investigational therapies. A recent *in vitro* study reported that lopinavir inhibits SARS-CoV-2 replication with a 50% effective concentration (EC<sub>50</sub>) of 16 720 ng/mL.<sup>1</sup>

Here we describe lopinavir pharmacokinetics in COVID-19 patients treated with ritonavir-boosted lopinavir at the Nantes University Hospital, France.

Patients receiving ritonavir-boosted lopinavir for COVID-19 at the Nantes University Hospital were included in this work without exclusion criteria. Concentration measurements were part of the routine. Plasma samples were collected at peak (4±1 h after intake) or trough (at least 10 h after intake in the case of 400/100 mg q12h and at least 18 h after intake in the case of 400/100 mg q24h). Samples outside these times were also measured. Ultrafiltration to obtain free protein plasma was adapted from a published method.<sup>2</sup> Ultrafiltration units (Millipore Amicon Ultra-0.5) were incubated with 5% Tween 20 at room temperature for 24 h before use to limit non-specific binding of drug to the device. Lopinavir concentrations were measured by an LC-MS/MS validated assay (ISO 15189) at the Nantes University Hospital. Drug safety, clinical and biological data were collected during patient hospitalization. Informed consent was obtained from each individual (or authorized representative) and ethics approval was

obtained from the Groupe Nantais d’Ethique dans le Domaine de la Santé (GNEDS).

Twelve patients (seven male and five female) were included. Median (range) age was 65.5 years (53 to 77 years) and median (range) BMI was 27.9 kg/m<sup>2</sup> (20.1 to 43.75 kg/m<sup>2</sup>). Eleven patients had COVID-19 confirmed by RT-PCR on nasopharyngeal samples and one had two negative RT-PCR tests but positive findings on chest CT images. Eleven patients were hospitalized in the infectious diseases department and three of them were secondarily transferred to the ICU because of severe acute respiratory syndrome. One patient was directly hospitalized in the ICU. During their care, seven patients (58%) received oxygen therapy. One patient died during their hospital stay. Ritonavir-boosted lopinavir was initiated in median (range) 4 days (1 to 9 days) after the first symptoms. Thirty plasma samples from the 12 patients were tested. Samples were collected from the first day after ritonavir-boosted lopinavir initiation to Day 5. Two patients received lopinavir/ritonavir 400/100 mg q24h, one patient q12h and then q24h and nine patients q12h. Patients in the infectious diseases department received tablets and ICU patients received oral solution by the nasogastric route. Regarding total lopinavir concentrations, median (range) peak concentrations in the q12h and q24h schemes were 18 150 ng/mL (15 600 to 26 500 ng/mL; n = 10 samples) and 28 400 ng/mL (n = 1), respectively, and median (range) trough concentrations in the q12h and q24h schemes were 18 000 ng/mL (11 400 to 30 800 ng/mL; n = 11) and 11 650 ng/mL (8740 to 18 300 ng/mL; n = 4), respectively (Figure 1). Regarding unbound lopinavir concentrations, median (range) peak concentrations in the q12h and q24h schemes were 159.7 ng/mL (112.7 to 273 ng/mL; n = 6 samples) and 109.1 ng/mL (n = 1), respectively, and median (range) trough concentrations in the q12h and q24h schemes were 160.3 ng/mL (93.1 to 287.3 ng/mL; n = 6) and 78.9 ng/mL (58.7 to 125.4 ng/mL; n = 4), respectively (Figure 1). The median (range) unbound fraction was 0.82% (0.38% to 1.52%; n = 21 paired samples). Median (range) ritonavir trough



**Figure 1.** Lopinavir concentrations in SARS-CoV-2-infected patients after ritonavir-boosted lopinavir 400/100 mg once or twice daily. Total (black) and unbound (grey) concentrations are represented by medians, IQRs and ranges at peak (4±1 h after intake) or trough (q12h: at least 10 h after intake; and q24h: at least 18 h after intake).

concentration was 307 ng/mL (78.3 to 1390 ng/mL), median (range) albumin serum level was 32.6 g/L (24 to 40 g/L;  $n=5$ ) and median (range) C-reactive protein (CRP) was 48.9 mg/L (19.4 to 157.5 mg/L;  $n=10$ ).

The most frequent adverse events related to ritonavir-boosted lopinavir were diarrhoea ( $n=6$ , including two cases with concomitant amoxicillin/clavulanic acid) and nausea and vomiting ( $n=2$ ). No severe adverse events were reported. In one patient secondarily admitted to the ICU for multivisceral failure (acute renal failure and acute respiratory distress syndrome), cytotoxicity more than 10 times that of normal (predominantly AST) led to discontinuation of lopinavir after 8 days of treatment.

Lopinavir concentrations in COVID-19 patients were extremely high compared with those usually observed in HIV-infected patients (trough: 18 000 ng/mL versus 5365 ng/mL with 400/100 mg q12h).<sup>3</sup> Lopinavir is metabolized by cytochrome P450 3A4 isoenzyme and it is well known that infection and inflammation are associated with down-regulation of cytochrome P450s.<sup>4</sup> It was reported that lopinavir concentrations varied with CRP levels in HIV patients.<sup>5</sup>

In our study, one patient receiving lopinavir oral solution by the nasogastric route was included (two trough concentrations: 25 500 and 23 000 ng/mL). It would be important to evaluate the influence of tablets versus oral solution on lopinavir pharmacokinetics in COVID-19 ICU patients.

Data about lopinavir pulmonary diffusion in COVID-19 patients are now necessary to compare with  $EC_{50}$  (epithelial lining fluid/plasma ratio of 1.77 in HIV patients).<sup>6</sup> We can note the good safety profile observed in our study, without any severe adverse events related to lopinavir/ritonavir. If lopinavir/ritonavir is still to be used in COVID-19, and until pharmacokinetics targets are better assessed, clinicians should only lower dosage based on clinical and biological safety criteria rather than only on plasma concentrations.

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## Transparency declarations

None to declare.

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